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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,787	CANTON ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-12,15-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,15-22 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/11/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I, claims 2-3, 11-12 and 21-22, in the reply filed on 8/16/2006 is acknowledged. The traversal is on the ground(s) that the search of all the claims should not impose any undue burden and both groups can be searched together. This is not found persuasive because the inventions are separate and distinct each from the other because the compounds of Groups I and II differ by a significant structural feature, having different formula IA and IB. Given the fact that chemical compounds that are not similar in structure have different physical, chemical, biological and physiological properties or activities, the instant compounds are deemed to have different modes of operation, different functions, and different effects. Moreover, it is noted that for example a prior art for the heterocyclic compound of formula (IA) would not be a prior art for the heterocyclic compound of formula (IB) under 35 U.S.C. 103(a). The requirement is still deemed proper and is therefore made FINAL.

Linking claims 1, 6-10, 15-20 and 25-28 are examined as drawn to the elected structural formula IA. Claim 4, 5, 13, 14, 23 and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/16/2006.

This application contains claims 4, 5, 13, 14, 23 and 24 drawn to an invention nonelected with traverse in Paper No. 8/16/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 recites limitations drawn to how the administration of the active agents is performed whereas parent claim 8 is drawn to a composition comprising a general class of active agents.

Claims 2, 11 and 21 are objected to because of the following informalities: Claims 2, 11 and 21 recite the term "quadrisaccharide". The use of the term "tetrasaccharide" is suggested since it is the art recognized term used to mean a oligosaccharide comprised of four monosaccharide units. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 8-12, 15, 17-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,019,023 ('023 patent); claims 1-3 of U.S. Patent No. 6,642,269 ('269 patent); claims 1-7, 9-15 of U.S. Patent No. 6,387,944 ('944 patent); claims 1-5, 11-12, 19-21, 23, 25, 27 and 29 of U.S. Patent No. 6,221,897 ('897 patent); claim 1 of U.S. Patent No. 6,107,494 ('494 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Instant Claims 1-3, 8-12, 15, 17-18 are drawn to compositions comprising compounds of formula IA with excipients, carriers or diluents and HMG-CoA reductase inhibitors.

Claims 1-4 of U.S. Patent No. 7,019,023 ('023 patent); claims 1-3 of U.S. Patent No. 6,642,269 ('269 patent); claims 1-7, 9-15 of U.S. Patent No. 6,387,944 ('944 patent); claims 1-5, 11-12, 19-21, 23, 25, 27 and 29 of U.S. Patent No. 6,221,897 ('897 patent); claim 1 of U.S. Patent No. 6,107,494 ('494 patent) are all also drawn to compositions comprising compounds of instant formula IA and excipients, diluents and carriers and HMG-CoA reductase inhibitor like statins.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that Instant Claims 1-3, 8-12, 15 and 17-18 are substantially overlapping with the claims of the patents as described above. One of ordinary skill in the art would be motivated to make compositions as instantly claimed since the structure and utility of the compounds and compositions as instantly claimed are same as that taught in the copending claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-12, 15-22 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease using the compound of formula IA and for compositions comprising compounds of formula IA and statins (HMG-C0A reductase inhibitors) and ezetimibe (cholesterol reductase inhibitor), does not reasonably provide enablement for the said treatment using a combination of the compound of formula IA and all other inhibitors that fall under the broad categories recited in claim 27 and also does not provide enablement for the compositions comprising a combination of the compound of formula IA and all other inhibitors that fall under the broad categories as recited in claims 8-9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The level of one of ordinary skill
(C) The amount of direction provided by the inventor
(D) The existence of working examples
(E) The level of predictability in the art

(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The recitation in claims 1 and 8, namely a composition comprising a biliary acid reuptake inhibitor and one or more compounds chosen from various other general classes of inhibitors is a broad recitation. The agents recited are also seen to reasonably include not only known compounds but also unknown compounds as of the filing date. The term prevention is seen to include the administration of the said compounds and inhibitors to a healthy mammal, and subsequent exposure to conditions that would cause the said disease/condition, wherein the said compounds prevent said exposure from manifesting itself in said mammal so exposed.

The level of one of ordinary skill in the art

The skilled artisan in this field is that of an MD.

The amount of direction provided by the inventor

In the instant case the general class of compounds recited in the instant claims is purely a functional distinction that reads on any known or unknown compounds that might have the recited functions. The specification (page 9) recites broad categories of compounds that may be used in the instant composition and method of treatment. The CAFC further clearly states "A written description of an invention requires a precise definition, such as by structural formula or chemical name, of the claimed subject matter sufficient to distinguish it from other materials. One skilled in the art therefore cannot visualize or recognize the identity of the members of the genus.

The existence of working examples

The working examples set forth in the instant specification are drawn to administration of compound of formula IA to transgenic mice and assaying beta amyloid peptide from the brain extracts. One of ordinary skill in the art will not extrapolate this to compositions comprising all other biliary acid reuptake inhibitors and one or more compounds chosen from various other general classes of inhibitors and to methods of treatment and prevention using the same since the examples provided are not representative of all of the therapeutic agents or combinations encompassed by the recitation of instant claims.

The level of Predictability in the Art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since on of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the combinations/compositions herein. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed., 1996, page 54, teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug-drug interactions

occurring with the many combinations of any compounds having the functional properties in the pharmaceutical combinations/compositions claimed herein. Thus, the teachings of Gillman and Goodman clearly support that the instantly claimed invention is highly unpredictable.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to represent all the combinations/compositions and the method of treatment or prevention encompassed by the recitation of the instant claims. One of ordinary skill in the art would have to carry out undue experimentation to practice the instant invention. Since any structural variation to a compound would be reasonably expected to alter is properties, one of ordinary skill in the art would be required to perform undue experimentation to determine which, if any, of the biliary acid reuptake inhibitors and all o the general classes of inhibitors would be useful to make a composition and the efficacy of the same in the said method of treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 8-12, 15-18, 21-22 and 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 11 and 21 recite the terms, "physiologically functional derivatives". In the absence of the specific derivatizations to the chemical core claimed or distinct language to

describe the structural modifications or the chemical names of the derivatives of this invention, the identity of said derivatives would be difficult to describe and the metes and bounds of the said derivatives applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated. It is also not clear what physiologically functional means.

Claims 3, 12 and 22 do not end in a period. It is not clear if the claim ends as recited or if any additional recitation is intended. The claims are rendered indefinite.

Claims 8, 17 and 27 recite the notations HMG-CoA and APP. It is not clear what applicants intend by these notations. In the absence of an expansion for these notations the claims are rendered indefinite. The expansion followed by the notation within parentheses should be recited at the first occurrence of the notations.

Claim 9 recites the limitations "separately or spaced out" in claim 8. There is insufficient antecedent basis for this limitation in the claim. Claim 8 is drawn to a composition wherein the active agents are in combined. A similar recitation is also seen in claims 18, 27 and 28.

Claim 10 is drawn to a compound comprising an effective amount of the active agents recited. In the absence of a recitation for the amount of the active agent it is not clear what constitutes an effective amount. The claim is rendered indefinite.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-12 and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Frick et al (US 6,221,897).

Frick et al teach compounds of formula I (col. 23, line 1 through col. 24, line 17), which is the same as the compound of formula IA as instantly claimed and pharmaceutical compositions comprising the compounds of formula I (col. 25, lines 57-59). This teaching is seen to read on instant claims 1-3. The suitable dosage is 0.02 to 50mg and the compositions are in a form for oral administration like capsules, tablets, etc. (col. 3, line 26 through col. 4, line 22). This teaching reads on instant claims 6-7. Fricke teaches compositions comprising the their compound of formula I in combination with statins (HMG-CoA reductase inhibitors; col. 26, lines 1-2; col. 3, lines 15-18). This reads on instant claims 8-9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-12 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frick et al (US 6,221,897) and Castaner et al (Drugs of the Future, 2000, 25(7), 679-685).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Frick et al teach compounds of formula I (col. 23, line 1 through col. 24, line 17), which is the same as the compound of formula IA as instantly claimed and pharmaceutical compositions comprising the compounds of formula I (col. 25, lines 57-59). Their compounds of formula I are also useful for lowering the serum cholesterol level (col. 3, lines 5-11). The suitable dosage is 0.02 to 50mg and the compositions are in a form for oral administration like capsules, tablets, etc. (col. 3, line 26 through col. 4, line 22). However, Fricke et al do not teach

compositions comprising their compound of formula I in combination with a cholesterol uptake inhibitor.

Castaner teaches that ezetimibe (page 679, formula shown at top left) is a potent cholesterol absorption inhibitor (page 682, right column, pharmacological actions through page 683, left and right columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (IA) and cholesterol absorption inhibitors to make a third composition comprising both the active ingredients in individually effective amounts since the both the active ingredients and their effective dosage is seen to be taught individually in the prior art of record.

It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose (In re Kerkhoven, 626 F. 2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Claims 18-22 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frick et al (US 6,221,897) in combination with Refolo et al (Neurobiology of Diseases, 2001, 8, 890-899).

Frick et al teach compounds of formula I (col. 23, line 1 through col. 24, line 17), which is the same as the compound of formula IA as instantly claimed and pharmaceutical compositions comprising the compounds of formula I (col. 25, lines 57-59). Their compounds of formula I are also useful for lowering the serum cholesterol level (col. 3, lines 5-11). The suitable dosage is 0.02 to 50mg and the compositions are in a form for oral administration like

capsules, tablets, etc. (col. 3, line 26 through col. 4, line 22). However, Fricke et al do not teach the use of the compounds and compositions of their invention for the treatment of Alzheimer's disease.

According to Refolo et al studies have shown that cholesterol may play an important role in the pathogenesis of Alzheimer's disease. A strong correlation between the amount of plasma cholesterol level and brain A-beta peptides and beta-amyloid was observed (page 890, abstract). These amyloid peptides are present in the neurite plaque of Alzheimer's patients (page 890, Introduction). However, Refolo et al do not teach or suggest the use of a biliary acid uptake inhibitor like compounds of instant formula IA for the said treatment.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat Alzheimer's disease in a patient by administering a compound of instant formula IA since it is known in the art that compounds of instant formula IA have hypochloesterolemic activity according to Fricke et al and cholesterol lowering drugs are shown to reduce beta-amyloid peptides that play a role in the pathogenesis of Alzheimer's disease.

One of ordinary skill in the art would be motivated to use compounds of instant formula IA in a method as instantly claimed in order to look for other more efficient hypochloesterolemic compounds. The skilled artisan would expect other hypochloesterolemic agents to work since reduction of cholesterol levels is associated with reduced amyloid peptides.

Conclusion

Claims 1-3, 6-12, 15-22 and 25-28 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

9/27/06

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